Salicylic Acid-Induced Local and Long-Distance Signaling Models in Plants

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Abstract Salicylic acid (SA) is one of the key hormonal factors determining the fate of plants exposed to stressful conditions, which is naturally found in plants and shown to be involved in the plant defense-related actions against infection by various pathogens. Recently, intracellular SA receptors were finally identified after a long survey of SA-binding proteins. In this chapter, the modes of both the short- and long-distance signaling events involving the actions of SA, a defense-related key signaling molecule, are compared by covering both the biochemical and electrophysiological views. Here, two distinct models for local SA perception and signaling mechanisms involved in the extracellular and intracellular paths (referred to as models i and ii), and the three different models for long-distance signaling mediated by SA are reviewed (referred to as models iii–v). The local SA signaling events can be attributed to (i) the extracellular SA perception model in which reactions between SA and apoplastic proteins result in acute oxidative burst

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followed by internalization of the derived signals via activation of calcium channels, and/or (ii) intracellular SA perception mechanism by which the action and life cycle of NPR1 protein are determined depending on the concentration of SA in both the infected cells and neighboring cells. On the other hand, the long-distance SA action could be attributed to three different modes, namely, (iii) local increase in SA followed by phloem transport of SA, (iv) systemic propagation of SA-derived mobile signals with both electrical and chemical natures without direct movement of SA, and (v) synergistic propagation of both SA and derived signals through the tissues and phloem. We view here that the long-distance SA signaling events (models iii–v) inevitably involve the mechanisms described in the local signaling models (models i and ii) as the key pieces of the puzzle.

Keywords Long-distance signaling • Phloem-mobile signal • Salicylic acid • Signal transduction

1 Introduction

Recent studies have elucidated that plant responses to different stresses are highly complex and involve the changes at physiological, cellular, and transcriptome levels (Atkinson and Urwin 2012). For finely geared controls of plant behaviors leading to homeostasis, plants are also equipped with stress-responsive signaling mechanisms as such mediated by hormonal regulations. Salicylic acid (SA) is one of the key phytohormones involved in both the abiotic (Kunihiro et al. 2011; Liu et al. 2012; Drzewiecka et al. 2012) and biotic (Vlot et al. 2008, 2009; Dempsey et al. 2011) stress adaptation.

For regulation of the growth and development within entire plant bodies, the long-distance signal translocation machineries are inevitable components because some of the local information or locally sensed input data such as wounding, viral infection, changes in nutritional condition, or water potential sensed by root hairs or stomata must be signaled to entire plant bodies to adapt to environments (Furuichi et al. 2007). Thus, locally targeted stimuli are rapidly converted to intracellular signals and then the re-generated extracellular signals by the stimulated cells are transferred to the parts or organs distant from the site of stimulus perception. One of the paths for long-distance signaling in plants is the highly systematized vascular bundle system which basically plays central roles in the absorption and translocation of water, minerals, and other nutrients to systemically support and maintain the growth of tissues and cells (Furuichi and Kawano 2006).

In this chapter, the modes of both the short- and long-distance signaling events involving the actions of SA, a defense-related key signaling molecule, are compared by covering both the biochemical and electrophysiological views. In the below sections, two distinct models for local SA perception and signaling mechanisms involved in the extracellular and intracellular paths (models i and ii),

and the three different models for long-distance signaling mediated by SA are reviewed (models iii–v).

The local SA signaling events can be attributed to (i) the extracellular SA action model and/or (ii) intracellular SA perception model. On the other hand, the long-distance SA action could be attributed to three different modes, namely, (iii) local increase in SA followed by transportation of SA, (iv) systemic propagation of SA-derived mobile signals with both electrical and chemical natures without direct movement of SA, and (v) synergistic propagation of both SA and derived signals through the tissues and phloem. This includes the alternately repeated secondary signal propagation and production and/or release of SA finally contributing to the systemic spread of SA-derived signals.

Although five different models (i–v) are reviewed here, some models can be considered as a part of one model. For instance, we view here that the long-distance SA signaling events inevitably involve the mechanisms or modes of SA actions described in the local signaling models as the key pieces of the puzzle.

2 Early Defense Signaling Models and Salicyl Acid

2.1 SA and Systemic Acquired Resistance

In the environments, living plants must respond to and combat a variety of stressful stimuli with biotic and abiotic natures, which often threaten the life of plants. Biotic factors menacing the plants include animal and insect herbivores (Barbehenn et al. 2010) and a wide range of pathogenic microbes such as viruses, bacteria, and fungi (Kerchev et al. 2012; Kangasjärvi et al. 2012).

SA is one of the key hormonal factors determining the fate of plants exposed to stressful conditions, which is naturally found in plants and shown to be involved in the plant defense-related actions against infection by various pathogens (Vlot et al. 2009). The name of SA and related compounds originally came from the *Salix helix* (willow), since they were discovered as the major components in the extracts from the tree barks of willow and also from poplar, which had been used as natural anti-inflammatory drugs over centuries until the eighteenth century (Rainsford 1984; Weissman 1991).

The first study focusing on the role of salicylates as disease resistance-inducing chemicals (White 1979; Antoniw and White 1980) revealed that treatment of the leaves of tobacco (*Nicotiana tabacum* L.) with aspirin (acetylsalicylic acid) drastically enhances the resistance to subsequent infection by tobacco mosaic virus (TMV). Later studies demonstrated that aspirin and SA induce systemic acquired resistance (SAR) represented by systemic accumulation of pathogenesis-related (PR) proteins in plants through activation of corresponding cellular signaling mechanisms (Malamy et al. 1990; Métraux et al. 1990; Kessmann and Ryals 1993; Fu et al. 2012).

2.2 *Oxidative Signaling Events Leading to Abiotic and Biotic Stress Adaptation*

Reactive oxygen species (ROS) are in fact inevitably produced as by-products from normal metabolic reactions including mitochondrial respiration, photosynthetic processes, and fatty acid metabolism (Møller 2001; Baker et al. 2006; Noctor et al. 2007). A common property of all ROS types is that they can cause oxidative damage to cellular components such as proteins, DNA, and membranes (Møller et al. 2007). The specificity of the biological response of living plant cells to ROS depends on the chemical identity of ROS, intensity of the signal, sites of production, and developmental stages (Del Río et al. 2002). Therefore, apart from their harmful action, generation of ROS could be potentially beneficial to living organisms depending on the conditions (Apel and Hirt 2004).

Induced production of ROS such as superoxide anion radicals ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($HO^{\bullet}$) at the cell surface or apoplastic space well known as the "oxidative burst" is one of the earliest events detectable during the incompatible interactions between plants and pathogens (Yoshioka et al. 2008). Three decades ago, Doke, a plant pathologist at Nagoya University (Nagoya, Japan), first reported on the involvement of ROS in the plant–pathogen interaction, after observing that infection by *Phytophthora infestans* in potato tubers causes the generation of $O_2^{\bullet -}$ at the host cells' plasma membrane (PM), only in the incompatible interactions (Doke 1983a). *P. infestans* is a typical pseudofungal species which is now classified within the class of Oomycetes (Subclass, Peronosporomycetidae; Order, Pythiales) that causes the serious potato disease known as late blight or potato blight.

A series of Doke's works (Doke 1983a, b, 1985) demonstrated for the first time that ROS generation occurs in plants upon attacks by a pathogenic microorganism and that the members of ROS possibly function as the chemical signals required for induction of hypersensitive response (HR) as typified by host cell death, now often referred to as plant apoptosis (Coll et al. 2011; De Pinto et al. 2012). Doke also demonstrated that the treatment of potato tuber protoplasts with the cell wall preparation from *P. infestans* effectively induces the oxidative burst, suggesting that chemical components derived from pathogenic microorganisms (elicitors) trigger the burst of ROS production in order to stimulate the plant defense mechanisms (Doke 1983b).

Nowadays, a number of active teams working on plant ROS biology are distributed worldwide and their studies concern numerous aspects of the plant physiology throughout the plants' life cycle (Yoshioka et al. 2008). ROS production is actually recognized as a common denominator to not only biotic stresses such as plant–microbe interactions and plant–herbivore interactions, but also abiotic environmental stressful conditions such as exposure to soil metals, high salinity, drought, high intensity light, and low or high temperature stresses that cause major crop losses worldwide (Kawano et al. 2001, 2003; Yamamoto et al. 2003; Mittler et al. 2011; Swanson et al. 2011; Yokawa et al. 2011).

Exposures to both biotic and environmental abiotic stresses reportedly increase the intra- and intercellular levels of H_2O_2 by modulating the finely elaborated ROS-detoxification and regeneration networks, composed of ROS-producing enzymes, antioxidant enzymes, and biosynthetic pathways for low molecular antioxidants, all responsible for maintaining the homeostasis of ROS levels under tight control (Bolwell et al. 2002; Del Río et al. 2002; Kawano 2003; Kotchoni and Gachomo 2006; Yoshioka et al. 2008). This allows ROS to serve as signaling molecules in regulation of plant metabolism and cellular signal transduction pathways activated in response to environmental stresses (Gechev et al. 2006; Mittler et al. 2011).

Accumulated pieces of evidence suggested that hormonal signaling pathways leading to development of SAR are regulated under controlled ROS production as observed for SA, abscisic acid, jasmonic acid (JA), and ethylene (Gaupels et al. 2011). Such ROS-mediated hormonal regulations might play some crucial roles in the cross talk between biotic and abiotic stress signaling (Kawano 2003; Ströher and Dietz 2006; Mori and Schroeder 2004). Although many components of oxidative signaling networks have recently been identified, the mechanisms for orchestrated control of the diversified ROS production mechanisms at different cellular sites through fine-tuning of ROS feedback control to meet the physiological requirements such as plant growth, development, stress adaptation, and programmed cell death (PCD) are now actively studied (Coll et al. 2011).

2.3 ROS-Triggered Calcium Signaling Events

As discussed in our previous review (Kawano and Furuichi 2007), early studies have indicated that SA is an oxidative signal inducer which is essentially involved in the development of SAR against various pathogens with various natures. In the early 1990s, it was proposed that SA signal transduction leading to SAR is mediated by ROS derived from H_2O_2, since SA binds and inhibits H_2O_2-detoxifying enzymes, catalase (Chen et al. 1993a; Durner and Klessig 1996) and ascorbate peroxidase (Durner and Klessig 1995). While the proposed enzyme inhibition models suggested the involvement of passive mechanisms supporting the increases in ROS, an active mechanism involving extracellular peroxidase and NADPH oxidase that directly generates ROS in the presence of SA was reported in the late 1990s as discussed below.

In addition to ROS, the changes in cytosolic free calcium ion concentration ($[Ca^{2+}]_c$) are another key factor of SA-mediated signaling, and certain number of reports indicated that an increase in $[Ca^{2+}]_c$ is essential for the action of SA during plant defense, since $[Ca^{2+}]_c$ plays roles as a secondary messenger for certain processes in plant defense mechanisms (Knight et al. 1991; Sanders et al. 1999). First data suggesting the involvement of Ca^{2+} during the action of SA was obtained after removal of Ca^{2+}. Inhibition of SA-dependent induction and accumulation of chitinase by depletion or chelation of free Ca^{2+} was observed in tobacco cells and

leaves (Raz and Fluhr 1992), and carrot cell suspension culture (Schneider-Müller et al. 1994).

Direct evidence for the actions of SA leading to rapid generation of ROS (especially $O_2^{\bullet -}$) and increase in $[Ca^{2+}]_c$ was obtained through experiments using $O_2^{\bullet -}$-specific chemiluminescent probe-treated and aequorin-expressing tobacco BY-2 cells (Kawano et al. 1998). Treatment of tobacco BY-2 cells with sub-mM order of SA resulted in rapid and transient generation of $O_2^{\bullet -}$, and in turn, $O_2^{\bullet -}$ triggered the influx of Ca^{2+} into the cells by stimulating the opening of ROS-responsive calcium channels. Further works have revealed that the SA-induced extracellular oxidative burst (generation of $O_2^{\bullet -}$) is catalyzed by apoplastic free and cell wall-bound peroxidases (Kawano et al. 1998; Kawano and Muto 2000). Peroxidase activity is often enhanced upon challenges by microbes and insects and induced enzyme activity contributes to production of semiquinone free radicals and quinones through oxidation of phenolics (Barbehenn et al. 2010). Thus, SA could be one of such active peroxidase substrates leading to the production of radical species, chiefly SA radicals, which are further converted to stable compounds while yielding ROS members as by-products (Kawano et al. 1998; Kawano and Muto 2000; Gozzo 2003). Interestingly, induced peroxidase activity in plants further contributes to protection of plants from insects by damaging the plant feeding caterpillars partly via post-ingestive phenol-derived radical production mechanisms in the midguts of larvae (Barbehenn et al. 2010).

2.4 SA Receptors Identified

Klessig and his colleagues have conducted a series of pioneering works on SA-binding proteins (SABPs), putative SA receptors. The first SABP isolated from tobacco was shown to be catalase (Chen et al. 1993a, b; Conrath et al. 1995). As discussed above, an idea came out from these works suggesting that the increases in H_2O_2 and/or other ROS derived from H_2O_2 may be the key events acting downstream of SA, since the binding of SA to purified catalase resulted in the inhibition of spectroscopically monitored decay of H_2O_2. Similarly, Kawano et al. (1998) have observed the SA-dependent inhibition of catalase in suspension cultured tobacco cells in vivo by monitoring the H_2O_2-dependent evolution of oxygen. However, contribution of SA binding to catalase in SA biology still remains uncertain. Similar model for SA binding to ascorbate peroxidase has been proposed, but this could be excluded from the candidate for SA-signaling mediators. Concerning the involvement of ascorbate peroxidase, both positive (Durner and Klessig 1995) and negative (Miyake et al. 1996; Kvaratskhelia et al. 1997; Tenhaken and Rübel 1997; Kawano et al. 1998, 2004a) views have been presented.

From tobacco, SABP2 was isolated as a putative SA receptor (Du and Klessig 1997) which is highly required for TMV-induced SAR development (Kumar and Klessig 2003), and finally its role as a SA-stimulated lipase (Kumar and Klessig 2003) or a methyl salicylate (SAMe) esterase that demethylates SAMe to produce

free SA has been determined (Forouhar et al. 2005). SABP3 isolated from tobacco was identified as a chloroplast-targeted carbonic anhydrase that shows antioxidative activity when expressed in yeast (Slaymaker et al. 2002). Since possible role of chloroplast as the site of SA biosynthesis is highlighted through the study of *Arabidopsis thaliana* sid2 mutant lacking the chloroplast-localized ICS enzyme (Wildermuth et al. 2001), we can expect that a SABP specifically localized in chloroplasts may play some key roles. As Shah (2003) has predicted in his review, chloroplasts and plastids might be the source of signals affecting the response to pathogens, by analogy to the mitochondrial roles in mammals. As expected, recent study has provided the molecular link between chloroplasts and the cytoplasmic-nuclear immune system. Nomura et al. (2012) have shown that (a) pathogen-associated molecular pattern (PAMP) signals are quickly relayed to chloroplasts and evoke specific Ca^{2+} signatures in the stroma, (b) a chloroplast-localized calcium-sensing receptor designated as CAS is involved in stromal Ca^{2+} transients and responsible for both the basal resistance and R gene-mediated hypersensitive cell death induced by PAMP, (c) CAS acts upstream of SA accumulation, and (d) CAS is involved in PAMP-induced expression of defense genes and suppression of chloroplast gene expression possibly via singlet oxygen ($^1O_2$)-mediated path.

Apart from SABPs, NONEXPRESSOR OF PATHOGENESIS-RELATED PROTEINS1 (NPR1) was identified as a key molecule involved in SA signaling. Importantly, SA actually regulates the conversion of NPR1 from an oligomeric form to a monomeric form that migrates from cytosol into nucleus (Mou et al. 2003) and phosphorylation of NPR1 for facilitating NPR1's recruitment to a Cullin3 (CUL3) E3 ligase, subsequently leading to proteasome-mediated degradation of NPR1 protein (Spoel et al. 2003). Recently, Klessig's group (Moreau et al. 2012) has stated that "despite identification of the aforementioned SABPs, SA's signaling mechanisms remain unclear" and continued that "considering SA's many roles in plants, these SABPs may constitute only a small portion of SA's targets; moreover, the SA receptor remained to be found" and introduced the model for NPR1-dependent defense responses involving novel SABPs (NPR3 and 4) recently proposed by Xinnian Dong's team. Thus, SA receptors acting in the intracellular space were finally identified after a long journey.

3 Apoplastic and Intracellular SA Perception Models

3.1 Intracellular SA Perception

Recent demonstration by Xinnian Dong and her colleagues (Fu et al. 2012) represents a major step forward in our understanding of SA signaling mechanisms during plant defense responses. Although NPR1 has been long known as a key player in most of the SA-mediated defense signal transduction, it does not appear to be an SA receptor since SA does not directly bind to NPR1. The recent

demonstration by Dong's team can be summarized that the NPR1 paralogues, namely, NPR3 and NPR4, are adaptor proteins for the CUL3 E3 ligase that specifically target NPR1 for degradation in an SA concentration-dependent manner (Fu et al. 2012). Since the npr3/4 single and double mutants reportedly show elevated levels of NPR1, it is viewed that NPR3 and NPR4 directly interact with and determine the fate of NPR1. The newly proposed model views NPR3 and NPR4 as SA receptors that differ in their affinity to SA. The newly proposed roles for SA are to disrupt the NPR1–NPR4 interaction, leaving NPR1 free from the NPR4-mediated degradation in the presence of low concentrations of SA (nanomolar range), and to promote the NPR1–NPR3 interaction, allowing NPR1 degradation when SA is excess (over micromolar range). Thus the signaling action of NPR1 is allowed only in the moderate range of SA concentration. This model explains the relationship between the homeostasis of NPR1 level and SA action at different concentrations. The above mechanism corresponds to the model (i) for intracellular SA perception and induced signaling.

3.2 Apoplastic SA Perception and Signaling Events

As discussed in the earlier sections, the first report connecting ROS and Ca^{2+} in plant SA signaling has reported the direct measurements of the SA-induced $O_2^{\bullet -}$ and the SA-induced increase in $[Ca^{2+}]_c$ in aequorin-expressing tobacco BY-2 cells (Kawano et al. 1998). Addition of SA to tobacco BY-2 cells reportedly resulted in rapid generation of H_2O_2 (Kawano and Muto 2000) and $O_2^{\bullet -}$ (Kawano et al. 1998), and a transient increase in $[Ca^{2+}]_c$ (Kawano et al. 1998), in this order. In the model, ROS actively triggers the influx of Ca^{2+} into the cells, and this early oxidative burst induced by SA was shown to be an extracellular event involving the action of extracellular free and cell wall-bound peroxidases (Kawano 2003).

Action of SA mediated by both the cell wall peroxidase-dependent ROS production and Ca^{2+} influx was also observed in *Vicia faba* epidermis (Mori et al. 2001) and the cell suspension-cultured *A. thaliana* (Kadono et al. 2010). Both SA-induced $O_2^{\bullet -}$ and chemically generated $O_2^{\bullet -}$ were shown to induce the closure of stomata, which is known as a Ca^{2+}-dependently regulated event studied in *Commelina communis* L. (Lee 1998), *V. faba* L. (Manthe et al. 1992; Mori et al. 2001), and *A. thaliana* (Khokon et al. 2011). The SA-induced stomatal closure in *V. faba* and Arabidopsis was reportedly inhibited by ROS scavengers and inhibitors of peroxidase such as salicylhydroxamic acid, suggesting the involvement of peroxidise-mediated redox signaling during the action of SA leading to stomatal closure (Mori et al. 2001; Khokon et al. 2011).

According to Chen et al. (2002), induction of a PR-protein (protein N) is differently regulated by the two distinct signaling mechanisms corresponding to high- and low-dose of exogenously supplied SA. The process which is dependent on the higher concentration of SA (ca. 200 μM) reportedly relays the SA signal to induce protein N through ROS production, Ca^{2+} signaling, and protein

phosphorylation, while lower dose (20 μM) of SA induces protein N via alternative mode of signaling independent from ROS, Ca^{2+}, and protein phosphorylation events.

The above local SA perception mechanism involving apoplastic oxidative burst and calcium signaling corresponds to the model (ii) for extracellular SA perception and induced signaling which may form the earliest signaling events upon treatment of plant cells with SA. In addition to extracellularly localized peroxidases, PM-localized NADPH oxidases known as respiratory burst oxidase homologues (RBOHs) are likely to be involved in the apoplastic SA-dependent ROS production model (Yoshioka et al. 2001).

3.3 Cross talk Between the Extracellular and Intracellular SA Perception Mechanisms via SA Transport

In earlier publications, we made an overview on the possible control of local and systemic SA levels through movements of SA "in" and "out" of the cells, tissues, and organs (Kawano et al. 2004a; Kawano and Furuichi 2007). As SA is produced inside the cells, the first step in SA movement is secretion of SA by the cells. Secretion of SA mediates the cell–cell interaction among neighboring cells, through the extracellular SA perception mechanism and also via intracellular SA perception mechanism after internalization of SA. Also in case of experimental SA treatment, exogenously applied SA (extracellular SA) must be internalized in order to elicit the intracellular SA perception mechanism. This SA internalization process and SA excretion process are likely under the control of the extracellular SA perception mechanism, thus potentially impacting the homeostasis for intracellular SA concentration.

According to the works by a Taiwanese group, SA smoothly moves in and out of the plant cells and these processes are finely regulated by ROS and Ca^{2+} (Chen and Kuc 1999; Chen et al. 2001). They showed that ^{14}C-labeled free SA added to tobacco cells in suspension can be rapidly absorbed by the cells (within 5 min), and with time the majority (over 90 %) of the radioactivity can be released back to the extracellular medium as free SA (by 5 h). In this model, de novo induction of SA excretion process reportedly takes place when the cells are exposed to a relatively high dose of SA (ca. 200 μM). Interestingly, this process requires the production of ROS and subsequent cascades of Ca^{2+} signaling and protein phosphorylation (Chen et al. 2001), confirming the roles for ROS-triggered calcium signaling events following the extracellular SA perception as described by Kawano and his colleagues (Kawano et al. 1998; Kawano and Muto 2000; Mori et al. 2001), in the systemic spread of SA. A possible mechanism for excretion of SA at cellular level was proposed (Chen and Kuc 1999; Chen et al. 2001). This model partially explains the mode of long-distance SA spread through cell-to-cell SA translocation reported by Ohashi et al. (2004). In addition to the mechanism of SA transport

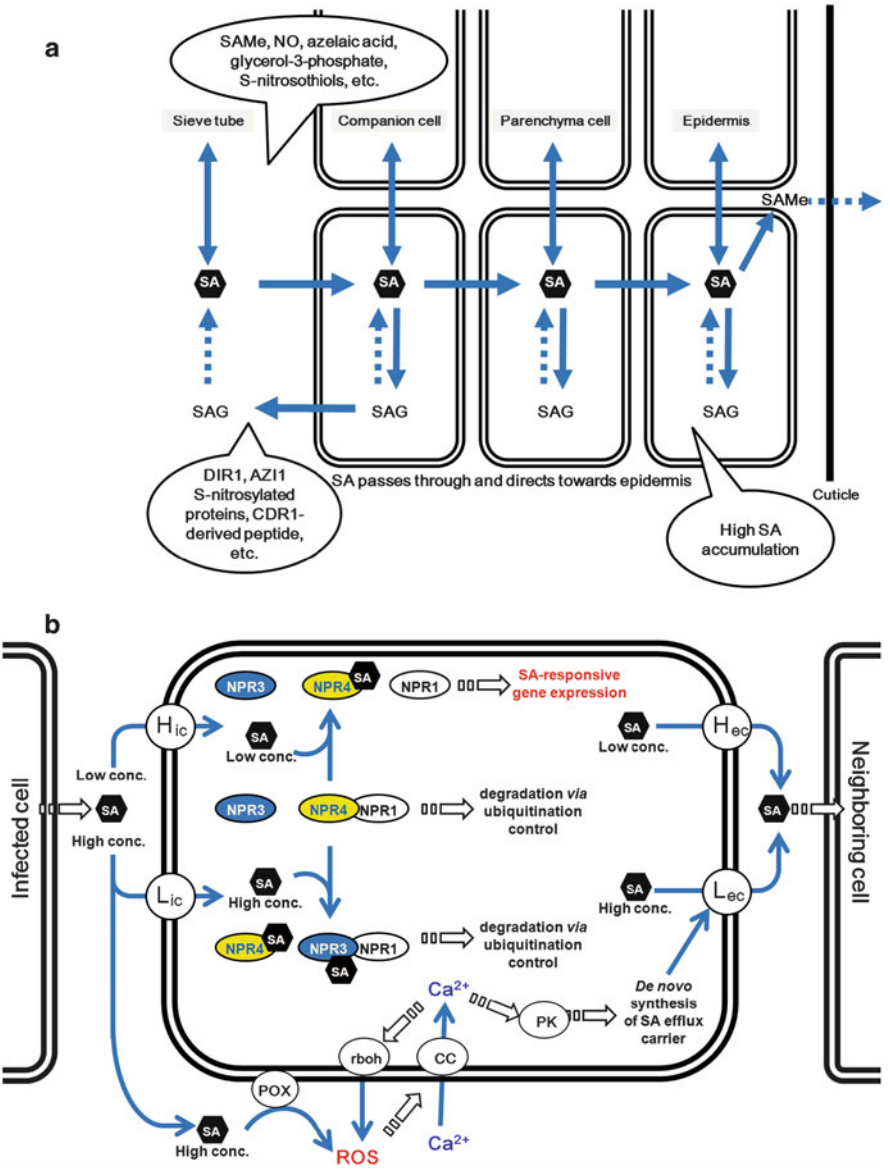

Fig. 1 Models for SA translocation at cellular and tissue levels. (**a**) Models for SA translocation in plants. Vertical movement of SA involving vascular transport and cell-to-cell transport is faster than horizontal movement of SA. In horizontal SA movement, cell-to-cell exchange of SA with preferential direction toward epidermis takes place. The cuticle layer is hardly permeable to SA under the physiological pH. *Arrows* represent the massive and rapid movement or interconversion of SA (to SAG and SAMe). *Broken arrows* indicate slower and minor paths of movement or interconversion. In addition to SA, SAG, and SAMe, putative mobile signals (both small molecules and proteins) contributing to development of SAR are listed. (**b**) SA concentration-dependent SA perception and SA

responsive to high dose of exogenous SA, there would be an alternative SA transport process responsive to low dose of exogenously applied SA (below 20 μM; Chen and Kuc 1999; Chen et al. 2001). The low-dose SA-responsive SA excretion process requires no de novo protein synthesis and is constitutively active independent of ROS, Ca^{2+}, and protein kinase. Thus, two distinct SA efflux carrier (s) constitutively present and newly produced in response to exogenous SA contribute to both the translocation and homeostasis of SA level in the cells (Kawano et al. 2004a). Figure 1 summarizes the modes of cell–cell and trans-phloem transports of SA and related chemical signals SA-dependently regulated in the pathogen-challenged plant tissue.

In *Arabidopsis* cells, a pH-dependent SA transport system has been reported (Clarke et al. 2005). Accordingly, SA is rapidly taken up by Arabidopsis cells, and SA uptake coincides with the alkalization of media and acidification of cytosol, and SA uptake was shown to be inhibited by the ionophore nigericin, suggesting that SA import is driven by a proton gradient. Importantly, against the ongoing $[H^+]$-dependent SA import, SA was shown to be exported back into the media as free SA after initial uptake of SA (Clarke et al. 2005). As mentioned earlier, the SA transport model through the cells reported in tobacco cells was also confirmed in Arabidopsis cells.

Since the above SA transport system is dependent on extracellular pH, homeostasis of extracellular pH could be the target of pathogen challenges combating against the systemic spread of defense signals chiefly SA, especially during incompatible plant–pathogen interactions. From this view point, Clarke et al. (2005) have investigated how SA transport may be modulated during incompatible defense responses by employing the bacterial harpin Pss as a model elicitor. As expected, harpin induced a rapid and sustained alkalization of the cell suspension media, reaching the critical pH (pH 5.9–6.1), and importantly, under this condition, SA import was shown to be inhibited for ca. 1 h.

The pH-dependent SA transport system was also found in mammalian cells such as human trophoblast cells, human choriocarcinoma cell lines, and hamster cheek pouch mucosa cells. The presence of carrier-mediated SA absorption mechanism has been elucidated by tracing the fate of ^{14}C-SA (Utoguchi et al. 1999; Emoto et al. 2002) and expression of SA-efflux transporter mRNA (Ikeda et al. 2012). In these animal models, SA influx carriers pH-dependently support the uptake of SA by cells

Fig. 1 (continued) translocation. Incorporation of low-dose and high-dose SA determines the action and fate of NPR1 through binding to NPR4 and/or NPR3. SA excretion mechanism responsive to high-dose SA reportedly requires the generation of ROS and subsequent Ca^{2+} and protein phosphorylation signaling cascades. The SA excretion mechanism responsible for low-dose SA is constitutively active independent of ROS, Ca^{2+}, and protein phosphorylation, requiring no de novo protein synthesis. L_{ic} and H_{ic}, low-affinity and high-affinity SA-influx carriers, respectively. L_{ec} and H_{ec}, low-affinity and high-affinity SA-efflux carriers, respectively. *CC* calcium channel, *PK* protein kinase, *POX* peroxidase. For details, see main text

and tissues both in vivo and in vitro, requiring low extracellular pH and higher intracellular pH, thus sensitive to protonophores and NaN_3. In contrast, a pH-independent SA uptake across the basolateral membrane of Malpighian tubules which is mediated by a non-electrogenic, α-cyano-4-hydroxycinnamic acid-sensitive, Na^+: salicylate co-transport system has been elucidated by tracing the fate of orally applied ^{14}C-SA in *Drosophila melanogaster* (Ruiz-Sanchez and O'Donnell 2006).

4 Models for Long-Distance Signaling

Generally, the long-distance signaling events in plants are possibly manifested through transport of active signaling molecules, the relays and exchanges of signals (or migration of secondary signals faster than the spread of signal-triggering molecules) without direct movement of the signal-triggering molecules, or combination of secondary signaling events followed by systemic production of the signal-triggering molecules.

In addition to two distinct local SA perception models (i) and (ii), we wish to propose that the long-distance SA action could be attributed to three different modes, namely, (iii) local increase in SA followed by transport of SA, (iv) systemic propagation of SA-derived signals with both electrical and chemical natures without direct movement of SA, and (v) alternately repeated secondary signal propagation and biosynthesis of SA and/or conversion of inert SA intermediates to free SA finally contributing to the systemic spread of SA-derived signals.

4.1 Long-Distance SA Transport

The induction of SAR following a localized infection must be mediated by some kinds of long-distance communication mediators moving through the phloem since earlier demonstrations showed that blocking of phloem transmission by stem girdling prevents the induction of SAR in leaves distal to the block (Delaney 2004). Later observations in tobacco and cucumber suggested that SA shows upward migration from the site of infection to the upper noninfected leaves through phloem (Métraux et al. 1990; Rasmussen et al. 1991; Yalpani et al. 1991).

In TMV-resistant Xanthi-nc tobacco, SA levels increase systemically after the single leaf inoculation with TMV. By tracing the $^{18}O_2$-labeled SA produced in TMV-infected leaves of Xanthi-nc tobacco, systemic spread of SA was observed (Shulaev et al. 1995). Similarly, Mölders et al. (1996) have shown that radioactivity of ^{14}C-labeled benzoic acid applied together with tobacco necrosis virus (TNV) to cotyledons of cucumber seedlings can be transported through phloem to upper leaves only after conversion to ^{14}C-SA. This study has concluded that SA rather

than its precursor is translocated from the site of virus inoculation to the upper young leaves, finally leading to the development of SAR.

Ohashi's team has examined the possible mechanisms for SA translocation and interconversion between SA and SA derivatives such as salicylic acid β-glucoside (SAG) and SAMe at cellular level leading to systemic spread of SA in tobacco plants, and concluded that vertical movement of SA involving vascular transport and cell-to-cell transport is faster than horizontal movement of SA (Seo et al. 1995; Ohashi et al. 2004). In horizontal SA movement, cell-to-cell exchange of SA with preferential direction from phloem toward epidermis takes place. As the cuticle layer is hardly permeable to SA under the physiological pH, massive movement of SA in horizontal direction ends there unless converted to SAMe.

Niederl et al. (1998) has evaluated the role of cuticle as the barrier at the plant surface for preventing the passive penetration of SA. Their work has shown that ^{14}C-SA hardly penetrates through the specific path on the cuticle, which is utilized for water penetration, thus this path allows no or negligible level of SA transport at normal physiological range of pH (between 3 and 6). This was also confirmed by Ohashi et al. (2004). Notably, the suggested form of the SA derivative which is active in cuticular penetration was shown to be SAMe, suggesting that methylation of SA is one of the key steps allowing pH-independent diffusion of SA-related molecules across the outer physical barriers of plants (Niederl et al. 1998). Emission of this volatile derivative of SA may partially contribute to the long-distance SA signaling events.

Using ^{14}C-labeled SA, without inoculation with pathogen, Ohashi et al. (2004) observed that translocation of SA is unexpectedly rapid when artificially applied onto the cut end of petiole from young and adult tobacco plants. When the spread of ^{14}C signal was monitored after feeding of ^{14}C-SA to the petiole end of the adult plants with expanded leaves, the signal reached the six neighboring upper leaves and three adjacent lower leaves within 10 min, and accumulated throughout the plant body in further 50 min in each replicate. Data also suggested that the majority of SA migrate as free form rather than glucosylated form SAG, especially in the early phase of SA translocation (within 10 min after SA addition). Thus SAG is a storage form requiring conversion to free SA in order to be translocated and utilized at the site of SA action. As mentioned above, capacity for rapid translocation of free SA inside the plants is high enough to allow the systemic spread of SA within short period. The above phenomena may fulfill the model (iii) for long-distance SA transport following the local increase in SA.

Controversially, an experiment opposing to the view that SA is a vascular-mobile signal in induction of virus-induced SAR was also obtained (Vernooij et al. 1994). Grafting experiments with wild-type and transgenic tobacco plants showed that *NahG* root-stocks (lacking SA accumulation due to expression of a bacterial SA-degrading enzyme) inoculated with TMV were fully capable of delivering a signal allowing the non-transgenic parts to resist the secondary TMV infection, suggesting the presence of additional vascular-mobile SAR-inducing signal(s) which is not SA. Although the above experiment was elegantly designed, the results must be dealt with caution since *NahG* transgene merely contributes to

the removal of SA without affecting the SA biosynthesis, and therefore, a small amount of residual SA can be found in *NahG* plants (Delaney 2004).

4.2 Long-Distance Communications by SA-Derived and SA-Induced Secondary Signals

Systemic signals are perceived in distant plant tissues and initiate systemic stress resistance through priming or induction of defense responses (Thompson et al. 2012). Recently, the knowledge on such long-distance signaling has been documented through the studies on SAR, systemic acquired acclimation (SAA), and systemic wound response (SWR). According to the above studies, phloem is the likely path for systemic transmission or movement of signals associated with SAR, SAA, and SWR. Similarly to SAR induction following the challenges by pathogens, abiotic environmental stresses can be the triggers for SA-centered signaling cascade finally leading to SAA in the challenged plants.

There are common views that both plasmodesmata and phloem are the likely paths for the spread of ROS during oxidative burst (Miller et al. 2009; Suzuki et al. 2011). However, the evidence for traveling of SA-induced ROS through phloem contributing to the long-distance signaling is not strong enough to conclude their roles, despite the key involvement of ROS in local SA action leading to SAR and SAA (Alvarez et al. 1998; Thompson et al. 2012).

In search for SA derivatives possibly acting as SA-derived signals, Pastora et al. (2012) have employed the precursor ion scan methods using an electrospray ionization tandem mass spectrometric technique (a multi-residue method with, liquid chromatography quadrupole time-of-flight mass spectrometry (LC-Q-TOF) and liquid chromatography multiple-reaction monitoring (LC-MRM)) and identified SAG and salicylic acid glucosyl ester (SGE), a new member of SA intermediates, as SA derivatives present in *Arabidopsis* cells challenged by virulent *Pseudomonas syringae* pv tomato DC3000.

To date, the candidates for the chemical signals systemically transported through phloem leading to induction of SAR, thus detectable in sieve elements or sieve-tube exudates, include small molecules such as SA (Yalpani et al. 1991; Shulaev et al. 1995; Mölders et al. 1996; Rocher et al. 2006, 2009), SAMe (Park et al. 2007; Rocher et al. 2009), azelaic acid and azelaic acid insensitive 1 (AZI1) protein (Jung et al. 2009), nitric oxide (NO; Song and Goodman 2001), and S-nitrosothiols (Rustérucci et al. 2007). Tran et al. (2012) have recently reported that oxalate, the simplest dicarboxylic acid, behaves as one of the signaling molecules in ozone (O_3)-exposed *Arabidopsis* cells; it is likely that the mode of oxalate action is similar to that of the action of azelaic acid. Among simple dicarboxylic acids sharing structural similarity as $(CH_2)n(CO_2H)_2$ with differed n (0–8), only oxalate ($n = 0$) and azelaic acid ($n = 7$) showed $O_2^{\bullet -}$-generating activity in cell suspension cultures of tobacco and rice (Kawano and Bouteau, unpublished results). Therefore,

in addition to azelaic acid, we are focusing the possible role for oxalate as a mobile signal under oxidative stress in plants.

Macromolecules such as S-nitrosylated proteins (Rustérucci et al. 2007; Leitner et al. 2009), constitutive disease resistance 1 (CDR1)-derived peptide (Xia et al. 2004), and defective in induced resistance 1 (DIR1) protein accompanying the glycerolipid-derived compounds such as glycerol-3-phosphate are also listed as candidates for phloem mobile signals during SAR development (Maldonado et al. 2002; Nandi et al. 2004; Mitton et al. 2009; Chaturvedi et al. 2008, 2012; Chanda et al. 2011). These molecules are all related to the signaling actions or metabolism of SA.

Apart from the SA-dependent mechanism, another plant defense-related phytohormone often antagonizing to SA induces SAR, and JA was also found to be translocated through phloem (Li et al. 2002; Hause et al. 2003; Truman et al. 2007; Chaturvedi et al. 2008; Glauser et al. 2008; Koo et al. 2009; Robert-Seilaniantz et al. 2011). In addition to induction of SAR, JA also induces SWR in plants. Similarly, a polypeptide systemin also induces SWR by acting as a phloem-mobile signaling molecule (McGurl et al. 1992).

4.3 Possible Long-Distance Communications via RNA-Binding Proteins

As RNA-binding proteins (RBP) can control gene expression at both transcriptional and posttranscriptional levels, involvement of RBP in plants' response to pathogen infection with rapid reprogramming of gene expression would be a likely mechanism. Recently, a putative model for SA-induced immunity in Arabidopsis mediated by RBP has been proposed (Qi et al. 2010). Reportedly, *A. thaliana* RNA-binding protein-defense related 1 (AtRBP-DR1) is involved in resistance to *P. syringae* pv. *tomato* DC3000. Notably, susceptibility and resistance to the above-mentioned pathogen were enhanced in *AtRBP-DR1* loss-of-function mutants and *AtRBP-DR1*-overexpressed plants, respectively (Qi et al. 2010). AtRBP-DR1 could be a positive regulator of SA-mediated immunity, possibly acting on SA signaling-related genes at a posttranscriptional level since the free SA level was maintained at low in the *Atrbp-dr1* mutant and high in the *AtRBP-DR1*overexpression line, and *AtRBP-DR1* overexpression lines showed spontaneous cell death in mature leaves accompanied by higher mRNA levels of SA-inducible *SID2* and *PR1*. Furthermore, a putative RBP from Arabidopsis, glycine-rich RNA-binding protein7 (AtGRP7) has been shown to confer plant defense against *P. syringae* DC3000 and other diverse pathogens such as *Pectobacterium carotovorum* SCC1 and TMV (Lee et al. 2012).

Although, to date, the involvement of RBP transport in long-distance SA signaling is obscure, it is tempting to expect that long-distance RBP transport takes place in the systemic plant defense mechanism, by analogy to the models

reported for the macromolecular transport through phloem playing pivotal roles in viral protein propagation and endogenous plant-transport-mediated growth and development (Ruiz-Medrano et al. 2012). Delivery of RNA to distant tissues might reflect a mechanism used by plants to regulate developmental and defense processes (Jorgensen et al. 1998; Lucas et al. 2001). Data presented by Aoki et al. (2005) introducing phloem RBP from pumpkin into rice plants indicated that, in addition to passive shoot-ward bulk flow transport, a destination-selective process is involved in long-distance root-ward movement of proteins through protein–protein interaction in the phloem sap. Recent study also suggested a regulatory mode of the phloem transport of RBP that involves the protein phosphorylation events in order to form a stable phloem-mobile complex (Li et al. 2011).

4.4 Long-Distance Electric Signaling

In animal systems, chiefly in species with developed brains, studies have revealed that the environmental stresses are recognized and transmitted via neurons. At the sensory cells of neurons, external signals directly or indirectly activate a number of ion channels, thus allowing the flux of ions across PM. These events effectively result in rapid changes in membrane potential, and these electrical responses, termed action potentials, are utilized to convey the information to the brain.

Although plants possess no neurons morphologically comparable to that of the animal system, the generation of action potentials in plant materials has been well documented (Meimoun et al. 2009; etc.). Dating back to the late sixteenth century, the most pioneering researcher in the field of electrophysiology, Luigi Galvani (1737–1798) provided the first evidence for plant electric signaling (Galvani 1791). Alexander von Humboldt (1769–1859), a German natural scientist, concluded that both animals and plants possess the bioelectrical feature, and suggested that the excitability of plant cells could be involved in long-distance signal translocation in plants (Botting 1973). Today, we can name two distinct types of electrical signals in plants, viz. the rapid action potentials and slow variation potentials, to be initiated and propagated through the activation of mechanosensitive and voltage-dependent channels which permeate cations or anions (Furuichi and Kawano 2006).

As demonstrated by the group at the University of East Anglia, the most successful model for systemic electrical signaling in plants is a wound response, in which the electrical activity spreads from the site of wounding (e.g., chewing by insect at cotyledons of tomato seedlings) to the whole plants, finally leading to systemic expression of a series of defense-related proteins, proteinase inhibitors, that inhibit the digestion in insects (Wildon et al. 1989, 1992; Rhodes et al. 1996). According to the above works, the expression of proteinase inhibitors in the intact tissues distal from the directly wounded tissue was not inhibited when chemical translocation was inhibited by chilling of the petiole of wounded leaf, suggesting

that electrical potentials, caused by a transient activation of ion channels, are one of the main components for wound-inducible long-distance signaling.

As mentioned earlier, the electrical response in a single cell can be considered as the triggering event for long-distance propagation of electric signals; we would like to overview if SA can cause such electrical response. The following section describes the cases of SA involvement possibly stimulating the electrophysiological signaling path in abiotic stress-challenged plant cells.

5 Electrophysiological Actions of SA: Cases of Anion Channel and Calcium Channel Activations by Abiotic and Biotic Stresses

5.1 Plant Responses to Air Pollution

Ozone (O_3) produced by a complex series of photochemical reactions from primary precursors emitted as nitrogen oxides and volatile organic compounds is a major secondary air pollutant often reaching high concentrations in urban areas under strong daylight, and studies are now suggesting that a steep increase in global background concentrations of O_3 is in progress and thus the impact of atmospheric O_3 on plants including valuable crops might be severer in the future world (Ashmore 2005). Several studies have shown that exposure to O_3 elicits the production of ROS as key mediators of stress response in growing plants. The most widely accepted model describing the nature of O_3 toxicity/tolerance is the oxidative stress model in which generation of ROS and release of oxidation products are involved in the generation and propagation of toxic compounds throughout the plants (Fiscus et al. 2005).

Chronic expositions to low concentrations of O_3 reportedly show a negative impact on crop yields by reducing photosynthesis and growth, and moreover, inducing senescence in premature leaf of sensitive plants (Pell et al. 1997). On the other hand, acute and transient exposures to O_3 induce the development of O_3 lesions on the leaves (Kangasjärvi et al. 1994). The lesions induced by O_3 highly resemble PCD that takes place in HR in plant–pathogen interactions (Kangasjärvi et al. 2005; Overmyer et al. 2005; Pasqualini et al. 2003). Such localized cell death is a common feature of O_3 phytotoxicity and is generally thought to be initiated by strong oxidizing action of O_3 itself as well as by O_3-derived ROS intermediates (Schraudner et al. 1998).

By focusing on the induction of PCD-like cell death, Kadono et al. (2006) have examined the development of O_3-induced cell death in two suspension-cultured cell lines of tobacco derived from Bel-W3 (hypersensitive to O_3) and Bel-B (highly tolerant to O_3) and observed the difference in sensitivity to O_3 as observed in their original plants. As high production of $^1O_2$ and H_2O_2 in the O_3-sensitive Bel-W3 cells, but not in the O_3-tolerant Bel-B cells, was observed upon exposure to O_3

(Kadono et al. 2006) and ROS scavengers and chelators of Fenton reagents effectively rescued the cells from the PCD induction by O_3, involvements of $^1O_2$, H_2O_2, $HO^{\bullet}$, and redox-active metals such as Fe^{2+} in O_3-induced acute damages to the cells have been suggested.

5.2 SA Is One of the Hubs Mediating the Responses to Abiotic Stresses

Upon exposure to O_3, a rapid increase in $[Ca^{2+}]_c$ occurs in the plant cells (Clayton et al. 1999; Evans et al. 2005; Kadono et al. 2006; Tran et al. 2012). As the O_3-dependent increases in $[Ca^{2+}]_c$ is sensitive to treatment with Ca^{2+} chelators, ion channel blockers, and ROS scavengers, the ROS-dependently induced flux Ca^{2+} from the apoplast into the cells might play a role as a signaling path initiating the oxidative cell death (Overmyer et al. 2005; Kadono et al. 2006). Interestingly, it has been pointed that there are the similarities between the defense activation mechanism and O_3 response in plants (Sandermann et al. 1998; Kadono et al. 2010). In fact, in O_3-sensitive line of tobacco (Bel-W3), SA is known as a potential biomarker of PCD development induced in response to ground-level ozone under ambient conditions (Drzewiecka et al. 2012). The sequence of the events starting from ROS generation and induction of Ca^{2+} signaling finally leading to both rapid and long-lasting cellular responses such as PCD-like localized cell death, stomatal closure, and SAR-related gene expression largely resembles the SA-induced phenomena (Kawano et al. 1998, 2004a; Mori et al. 2001). At the molecular level, involvement of *NPR1* in O_3-induced cell death in *A. thaliana* has been demonstrated (see Fig. 2b; Kadono et al. 2010).

Abiotic stresses involving SA-dependent signaling events (*NahG*-sensitive and *NPR1*-dependent path) include metal toxicities as such observed in aluminum-treated cells of *A. thaliana* (Kunihiro et al. 2011). As mentioned earlie, molecular evidences on the involvement of SA in the plant abiotic responses have been recently provided and accumulated; thus our understanding of the SA signaling pathways and mechanisms by which SA performs its role as the mediator of stress responses has been largely advanced.

5.3 Activation of Ion Channels by SA

As the possible involvement of SA in responses to O_3 was suggested, Kadono et al. (2010) have compared the electrophysiological impact of O_3 and SA in the cells of *A. thaliana*. Both O_3 and SA induced a rapid but slight hyperpolarization of the cells followed by a larger depolarization event within a few minutes. The temporal changes in the PM potential and the changes in anion channel activity were

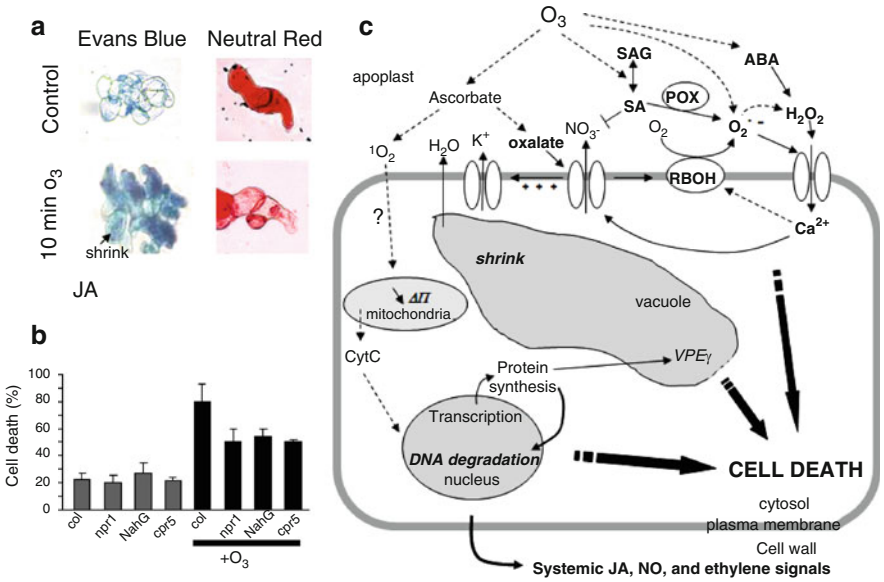

Fig. 2 Involvement of SA in the O_3-induced cell death in suspension cultured cells of *Arabidopsis thaliana*. (**a**) Microscopic images of O_3-induced cell death in wild-type cells (col) visualized after staining with Evans blue and Neutral red. (**b**) Effect of SA-related mutations on the O_3-induced cell death. (**c**) Hypothetical scheme for the action of SA interacting with ion channels and ROS-generating enzymes upon exposure to O_3, finally leading to PCD in *A. thaliana* cells. *CytC* cytochrome C, *VPEγ* vacuolar processing enzyme γ; Data and illustration are adapted from Kadono et al. (2010)

examined after treatments of the cells with O_3 and SA. As the delayed depolarization is correlated with an increase in anion channel activity, SA could not be responsible for the early depolarization induced by O_3, but SA can fuel the generation of H_2O_2 and Ca^{2+} influx involved in O_3-induced cell death. The SA-induced generation of H_2O_2 via stimulation of peroxidase and/or NADPH-oxidase is known to lead to Ca^{2+} influx (Kawano and Muto 2000; Kawano et al. 2004a) which could explain the delayed increase in anion currents observed in response to exogenous application of free SA. Upon stimulation, SA could be released from apoplastic SAG pool through the action of SAGase (Kawano et al. 2004b; Umemura et al. 2009).

As mentioned, SA was shown to be converted to electrophysiological signals correlated with biochemical changes leading to PCD development in Arabidopsis cells. As for future experiments, it is tempting to testify if these locally identified changes could be propagated as the chain of electric signal in the tissue as observed for SWR (Wildon et al. 1989, 1992; Rhodes et al. 1996).

5.4 Calcium Channels as a Target of Early SA Action

Electrophysiological studies have revealed that several types of Ca^{2+}-permeable channels are localized at PM and/or vacuolar membrane (VM) in many plant species (Jammes et al. 2011). Muto and his colleagues have attempted to isolate the cDNAs encoding for voltage-dependent Ca^{2+} channels (VDCCs) by expressing clones from a cDNA library of *A. thaliana* in the yeast *cch1* and *mid1* strains. Although this approach was not successful, a candidate for VDCC in plants, *AtTPC1* was finally isolated by the thorough search of the genomic sequence of *A. thaliana* using the 30–60 bp degenerated sequences from the partial amino acid sequences of several VDCCs in animal cells as the queries, and its Ca^{2+} permeability was tested in a *cch1* strain (Furuichi et al. 2001a). Sense–antisense experiments in *A. thaliana* and complementation tests in a Ca^{2+} uptake-defective yeast mutant have confirmed that *AtTPC1* might be functioning as a VDCC (Furuichi et al. 2001a). While no homologue of the major VDCCs has been isolated from plants to date (Jammes et al. 2011), the two-pore channel (TPC) family, originally found in rat (Ishibashi et al. 2000), was shown to be semi-homologous to vertebrate VDCCs sharing a half structure of the α1-subunit (Zhu et al. 2010).

Recent demonstration revealed that human TPCs mediate the nicotinic acid adenine dinucleotide phosphate (NAADP)-induced Ca^{2+} release from the acidic organelles in HEK293 cells (Calcraft et al. 2009). Prior to elucidation of the function of mammalian TPCs, plant biologists have shown that Arabidopsis's *AtTPC1* behaves as a slow-activating vacuolar cation channel (Peiter et al. 2005) which is involved in the sucrose-induced elevation of $[Ca^{2+}]_c$ (Furuichi et al. 2001b), extracellular Ca^{2+}-induced stomatal movement (Peiter et al. 2005; Islam et al. 2010), and abscisic acid-mediated prevention of seed germination (Islam et al. 2010).

Notably, *TPC1* family is the most likely group of VDCCs involved in ROS responses, assuming the well-conserved negatively charged residues within voltage-sensor (S4 of Shaker-units) are responsive to ROS-dependent voltage changes as previously demonstrated and reviewed (Kawano et al. 2004c; Kawano and Furuichi 2007). Orthologs belonging to the plant *TPC1* family were isolated from tobacco (Kadota et al. 2004) and rice (Hashimoto et al. 2005; Kurusu et al. 2004), and demonstrated to exist in some other plant species such as corn, broad bean, pea, spinach, and turnip (White et al. 2002; Kawano and Furuichi 2007). In *A. thaliana* and rice, such genes exist as single copy genes in the genome and are expressed in the entire plants, suggesting their systemic roles (Furuichi et al. 2001a, b; Kurusu et al. 2004). In tobacco BY-2 cultured cell line, there are two copies of genes with high similarity (97.1 % identity) with slightly different molecular masses (Kadota et al. 2004), apparently detectable with the specific antibody against *AtTPC1* (Kawano and Furuichi 2007).

Concerning the distortion of Ca^{2+} homeostasis by toxic ions in plants, it has been shown that action of Al^{3+} as a channel blocker specific for ROS-responsive Ca^{2+} influx (Kawano et al. 2003) is mediated by inhibition of *TPC1* channels (Kawano

et al. 2004c). Since the use of Al enables the dissection of *TPC1*-mediated ROS-responsive Ca^{2+} influx from the Ca^{2+} influx stimulated by other stimuli such as the mechano-sensitive nonselective cation channel-mediated osmotic stress-responsive Ca^{2+} influx, the involvement of plant *TPC1* channels in SA-induced and ROS-mediated Ca^{2+} influx in plant cells was tested (Lin et al. 2005). The inhibitory effect of Al^{3+} as a putative and selective blocker of *TPC1* channels supported the view that the *TPC1* type channels is involved in the SA-induced Ca^{2+} influx in tobacco BY-2 cells.

The roles of plant *TPC1* channels in overall defense response against the pathogens were further studied by several groups. Kadota et al. (2004) showed that *TPC1*s from tobacco (*NtTPC1*s) possess several physiological roles such as regulation of hypersensitive cell death and defense-related gene expression triggered by cryptogein, an elicitor from an oomycete, through elevation of $[Ca^{2+}]_c$ in tobacco BY-2 cells. In addition, *TPC1s* from rice and wheat appear to function in responses to abiotic stresses (Kurusu et al. 2004; Wang et al. 2005).

5.5 *Localization of TPC1 Channels in Plant Cells*

Molecular and electrophysiological studies have shown that Arabidopsis *TPC1* is mainly localized at the VM and functions as a slow-activating vacuolar cation channel (Peiter et al. 2005; Ranf et al. 2008; Dadacz-Narloch et al. 2011; Hedrich and Marten 2011). In contrast, TPCs in monocots including *OsTPC1* have been suggested to be localized at the PM and independently confirmed by several groups (Wang et al. 2005; Kurusu et al. 2005; Hamada et al. 2012; Hashimoto et al. 2005). Similarly, Kawano et al. (2004c) have reported the partial but significant localization of active *AtTPC1* fused with GFP at the plasma membrane when expressed in tobacco BY-2 cells. Thus, the presence of minor TPC1 population in PM should not be ignored as there would be physiological roles in both forms of TPC1 proteins localized in VM and PM.

6 Conclusions

In this chapter, the modes of the local and long-distance signaling events involving the actions of SA are compared by covering both the biochemical and electrophysiological views. Especially, we aimed at outlining the modes of SA action by allocating the newly elucidated model for the action of two SA receptors, NPR3 and 4, involved in regulation of NPR1's action and life cycle, in addition to the previously known SABPs and SA-reacting enzymes.

Here, two distinct models for local SA perception and signaling mechanisms, namely, the extracellular and intracellular paths, are listed. One of local SA perception model responsive to extracellular SA involves the ROS-generating

reaction catalyzed by apoplastic (cell wall-bound and free) peroxidases and PM-localized RBOHs followed by calcium signaling. The other local SA perception mechanism is responsive for intracellular SA, by which the action and life cycle of NPR1 protein are regulated depending on the concentration of SA in the cells. The model with NPR1 paralogues clearly explains how NPR1 escapes the ubiquitination-controlled turnover active in the absence and in the presence of excess level of SA in the cells. The intracellular and extracellular SA signaling mechanisms are likely linked through the import and export of SA by the cells. Since the low-affinity SA efflux carrier required for excretion of highly accumulated SA is reportedly induced by extracellular SA-induced oxidative burst and calcium signaling mechanism, the involvement of NPR4 could be minimized by enhanced SA efflux.

We view here that the long-distance SA signaling events inevitably involve the components in the local SA perception and signaling mechanisms. Here, three different models of SA mediated for long-distance signaling are described. The long-distance SA action could be attributed to the phloem-mediated and cell–cell transports of SA following the local increase in SA in the pathogen infected cells, SA-derived mobile signals with electrical and chemical natures systemically propagated without direct movement of SA, and synergistic propagation of both SA and derived signals throughout the tissues and phloem.

As known, long-distance signaling models also predicted the involvement of electrophysiological events at the site of the initial signal perception followed by systemic long-distance relaying of the electrically detectable signals; the last part of this article was used for reviewing the actions of SA on activation of ion channels such as anion channels and calcium channels. Electrophysiological models are also examples of our views that the long-distance SA signaling events inevitably involve the components or events in the local SA perception and signaling events.

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